Review Article

Feasibility of local administration of chemotherapeutic drugs as an effective adjuvant therapy in primary, recurrent and metastatic extradural tumours of the spine—review

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Abstract: Present day multimodality treatment with advances in systemic chemotherapy and radiotherapy has increased the survival of patients significantly even in those primary tumours which were once considered to have a poor prognosis. However, local recurrence can severely jeopardise the quality of life and even reduce survival. Hence local recurrence is considered as the worst complication in the management of spinal tumours and the need to achieving adequate local tumour control cannot be overemphasised. Techniques like en bloc resections which significantly reduce the chances of local recurrence are always not possible due to anatomical and technical reasons and sometimes, not feasible in debilitated patients. Local administration of chemotherapeutic drugs has already been recognised as a treatment strategy in the management of bladder and brain tumours. In this literature review, an attempt is made to explore the available evidence in the English literature for local administration of chemotherapeutic drugs in the surgical management of primary, recurrent and metastatic spinal tumours.

Keywords: Spine; tumour; chemotherapy; intraoperative; local

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Background

Primary epidural spine tumours constitute 10% of the tumours that involve the bony spine (1). Spine is also a common site for metastasis seen in up to 40% of cancer patients. 10% to 20% of patients with spinal metastasis develop paralysis (2-4). Local recurrence has been estimated to occur in 10% to 20% of these patients (5-7) and is considered as the worst complication in the management of spinal tumours as it significantly affects the quality of life and prognosis. This highlights the importance of achieving good local control in the management of spine tumours (8). Present day multimodality treatment with advances in systemic chemotherapy and radiotherapy has increased the survival of patients significantly even in those primary tumours which were once considered to have a poor prognosis. However, local recurrence can severely jeopardise the quality of life and even reduce survival. Thus, it is imperative that we attain tumour control to the maximum extent possible during the index surgery to reduce the chance of recurrence. *En bloc* resections with negative margins have been shown to have the least recurrence following surgery for primary and metastatic spine tumours. Nevertheless, *en bloc* resections are always not possible in the management of spine tumours due to the anatomy and close vicinity to the cord and major blood vessels and are often intolerable in those patients with co-morbid conditions and limited life expectancy (6,9-11). Thus, in those instances where the excision was intralesional or with evidence of breach of tumour margin, a local strategy to cause destruction of residual tumour cells is highly desirable. Systemic chemotherapy is often not the first line management for spine tumours and metastasis because of the fear of side effects that would occur even before therapeutic levels could be reached in

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Local administration of chemotherapeutic drugs following en bloc or intralesional resection of primary or metastatic primary tumours, including recurrent tumours
Published in the period from Jan 2000 to June 2018
Selected studies which were published before 2000
Exclusion criteria
Non spine tumours
No local administration of chemotherapy attempted

the bone (12,13). In such instances, local administration of chemotherapy might be an attractive option to ensure eradication of remaining tumour cells after excision. Any such attempt to reduce the chance of recurrence could have a significant positive impact on the functional and quality of life measures, even though it may not significantly affect the overall prognosis in patients as it is predominantly based on the extent of systemic spread (14). Local treatment has already been recognised as a treatment strategy in the management of bladder cancer with Bacillus Calmette-Guerin (BCG) (15), gliomas in the brain with intratumoral or intracavitary chemotherapy (16,17) and in hepatocellular carcinomas with percutaneous ethanol or chemoembolisation (18). Similar strategies are also being investigated in the other visceral cancers like the lung. Nevertheless, local administration of chemotherapy still largely remains as an unexplored treatment alternative with few available literatures already supporting its efficacy as an effective adjuvant therapy.

Objectives

The objectives of the present review are to look for evidence in the English literature on

(I) The efficacy of local administration of chemotherapeutic drugs in the management of primary and metastatic spine tumours;
(II) The suitability of chemotherapy drugs for local administration following surgical treatment of primary and metastatic spine tumours;
(III) The suitability of the delivery methods for local administration of chemotherapy;
(IV) The possibility of failure mechanisms and adverse effects following this technique.

Methodology

Search strategy—a comprehensive review of the English literature was performed using PubMed, MEDLINE, EMBASE, SCOPUS, Google Scholar, Web of Knowledge, Biomed Central and Cochrane Database of Systematic reviews. Search terms included the MeSH terms/keywords: "perioperative", "local administration", "intratumoral", "intracavitary", "interstitial", "chemotherapy and related terms" and "spine tumours".

When we began the literature search, we intended to conduct a proper systematic review and applied the inclusion and exclusion criteria as described in *Table 1*. We initially searched for studies only which used local administration of chemotherapeutic drugs in primary and metastatic spine tumours in humans. As only one case series study could be found, we relaxed our inclusion and exclusion criteria to include the animal studies and recurrent tumours as well and present our findings only as literature review. For the purpose of this review, only studies involving local administration of chemotherapeutic drugs for the management of spinal tumours were included. Data relevant to the research questions were recorded in tabular form.

Results

The initial search of PubMed, MEDLINE, EMBASE, SCOPUS, Google Scholar, Web of Knowledge, Science Direct, ProQuest, Sage, Biomed Central and Cochrane Database of Systematic reviews resulted in 712 references. After applying the inclusion and exclusion criteria (*Table 1*) and reviewing the full text articles, 4 animal studies on extradural metastatic spine disease, 1 human case series on spinal liposarcoma and 2 human case reports on recurrent extradural spinal tumours were found to be relevant (*Figure 1*).

Discussion

Skeletal tissue is one of the most frequent sites for metastasis of malignant tumours. Survival of metastasis patients is directly correlated with osseous involvement especially spinal cord compression (19-21). Perioperative local administration of chemotherapeutic drugs has many theoretical advantages. (I) It avoids the systemic side effects of systemic chemotherapy which includes myelosuppression, cardiotoxicity, renal toxicity, infection and gastrointestinal side effects. Previous studies have

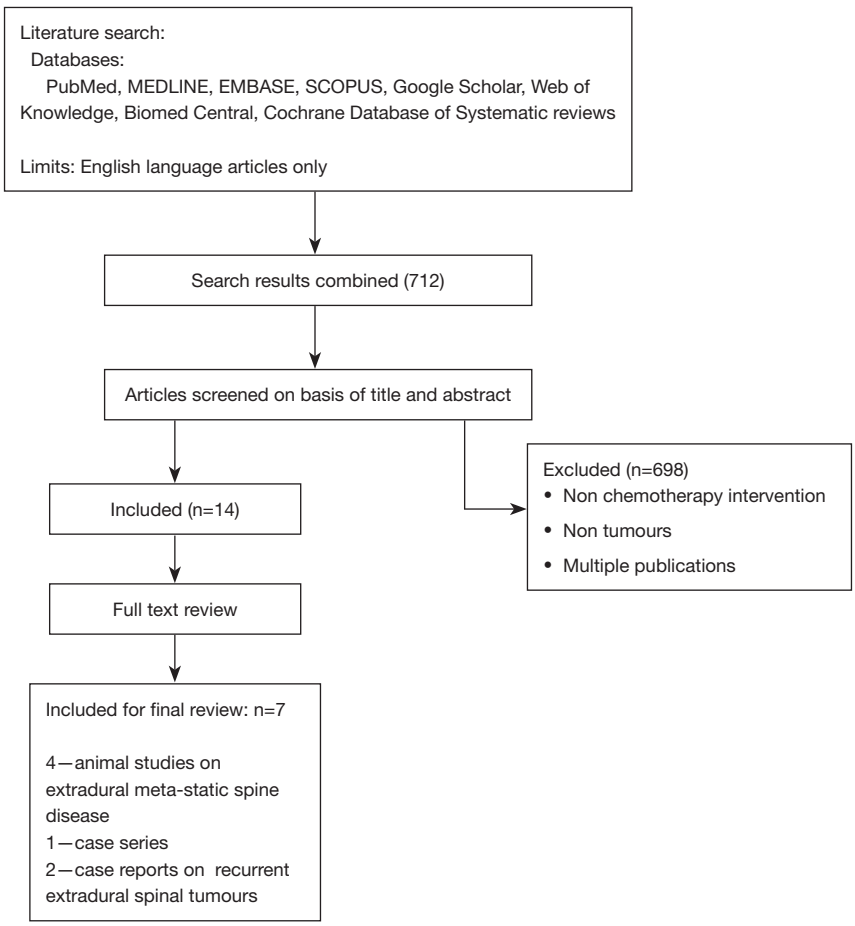

Figure 1 Flowchart of literature search.

shown that high systemic levels of chemotherapy drugs do not reach an effective concentration in tumours (22). Therefore, there is a possibility that high systemic levels of a chemotherapy drug often lead to systemic toxicity without even achieving cytotoxic concentration locally at the tumour area; (II) it avoids the organ damage from chemotherapy drugs and reduces the incidence of chemotherapy induced secondary cancers especially in children; (III) it achieves a high concentration of chemotherapy drug within a tumour and increased exposure time for a tumour to the drug which cannot be achieved by systemic therapy, thereby maximising the clearance of tumour cells. As only 10% to 15% of tumour cells are believed to be in the active replication phase at any time, an increased exposure time of the tumour to the drug is important to kill the residual tumour cells which replicate at different points of time (23,24); (IV) it is especially useful in drugs which have a shorter half-life or gets cleared from the body sooner. For instance, Carmustine has a shorter half-life of 15 min. But by sustained delivery systems, tumoricidal concentration can be achieved for up to 21 days in animal models (25); (V) it can potentially avoid the need for postoperative chemotherapy and radiotherapy and may reduce the health care costs associated with chemotherapy and radiotherapy; (VI) some chemotherapeutic drugs like paclitaxel have radiosensitising properties which blocks tumour cells in the radiosensitive phases of cell cycle (G2M phase). This technique which ensures a high concentration of drug close to the operated site is most likely to increase the benefits of subsequent radiotherapy (26,27); (VII) single time application of chemotherapy drug and thereby resulting in less wastage of drug (24).

However, this technique is not without any limitations which include: (I) high concentration of the drug is seen close to the delivery device or the site of administration and those tumour cells away from the device may escape from

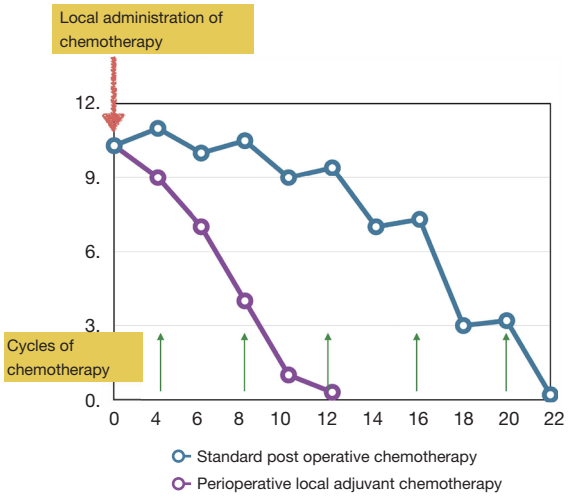

Figure 2 Comparison of residual tumour cell growth kinetics after excision in systemic *vs*. local chemotherapy.

the effect of the drug. This limitation can be mitigated to some extent through controlled drug-eluting device; (II) non-uniform distribution of drugs within the residual tumour mass or target region; (III) complications like wound healing problems, chemical and bacterial meningitis and subdural empyema have also been reported in animal (28) and human studies (29).

Rationale for using chemotherapy locally as an adjuvant therapy following excision

Human cancers follow Gompertzian model of growth as opposed to the log-kill kinetics which was once popular during the early years of the modern chemotherapy era. Log kill kinetics model was based on the belief that tumour growth is logarithmic, with the ratio of proliferating cells to total cells being constant. As a result, cell death is proportional regardless of tumour burden. However, this model became unpopular later as most human cancers were found to not follow purely exponential growth (30). Rather they follow the Gompertzian model of growth in which the ratio of proliferating cells to total cells reduces with increasing tumour size with a resultant exponential decline in growth fraction over time. Thus, in this model, chemotherapy which targets rapidly multiplying cells, kills an only small fraction of cells when the tumour is large and advanced but on the other hand, kills a larger fraction of cells when the tumour is small or clinically undetectable. This is especially important in the scenario of residual tumour cells which regrows following excision (31). The microscopic or macroscopic tumour deposits following excision have higher growth fraction resulting in faster regrowth of tumour. The residual tumour cells continue to multiply till the time they are attacked by the adjuvant therapy (chemotherapy or radiotherapy) which are usually given in cycles rather continuously to evade the systemic effects from them. Also, residual cells continue to multiply when they are not exposed to the chemotherapy drugs as in the time interval between the cycles. This limitation is likely to be surpassed when chemotherapeutic drugs are administered locally following surgical excision of tumours allowing no time for the tumour cells to multiply due to constant exposure to the drug leading to a steeper decline in the actual tumour burden.

Figure 2 details the theoretical possibility of residual tumour cell growth kinetics following surgical excision when exposed to the chemotherapy drugs locally.

Local administration of chemotherapeutic drugs—is it an effective adjuvant therapy for the management of spine tumours?

Table 2 lists the various studies where local administration of chemotherapeutic agents has been studied in relation to the management of spine tumours. At the time of writing this review, only 4 animal studies, 2 case reports and 1 case series were found in relation to the management of spine tumours despite repeated extensive literature search. Abe *et al.* in his 2007 and 2008 spine metastasis rat model study, demonstrated a statistically significant improvement in the disease-free time and survival when treated with paclitaxel-eluting drug delivery device (6,32). Bagley *et al.* also established a similar benefit with no systemic toxicity in breast carcinoma metastasis rat model when treating with a different drug delivery device eluting paclitaxel (33). Another study which implanted local administration of paclitaxel as adjuvant therapy in a breast carcinoma metastasis rat model showed added benefit in those rats where this technique was used in combination with surgery and radiotherapy than in those treated with surgery and radiotherapy alone (14).

The following study mentioned the use of intraoperative chemotherapy. Zhao *et al.* reported a case series of 7 patients with spinal liposarcoma who were managed surgically with resection and reconstruction. One *en bloc* resection and six piecemeal resections were performed. All patients had intraoperative chemotherapy with cisplatin with the aim to

Table 2 Studies on local administration of chemotherapeutic drugs

N	Study	Type	Details about study	Results	Conclusions
Extradural spinal tumours					
1	Abe T, 2007	Animal study, murine	Intraosseous spinal cancer rat model using paclitaxel loaded hydroxyapatite alginate gels	Disease free time and survival longer in local treatment group (P<0.05)	Local treatment with paclitaxel loaded hydroxyapatite alginate gels prolonged disease free time and survival rate
			Ten rats randomised into 2 groups	Local treatment group: survival =21.6 days, disease free time 20.8 days	No signs of systemic toxicity noted
			Group 1—local treatment group	Control group: survival =14 days; disease free time =11.8 days	
			Group 2—control group		
			Hindlimb motor function using BBB scale		
2	Bagley, 2007	Animal study, murine	Breast adenocarcinoma metastatic spine tumour model using OncoGel (paclitaxel releasing biodegradable polymer ReGel)	Better hindlimb function scores and longer survival in OncoGel 3.0% & 6.0% group than in control group (P<0.05)	Oncogel demonstrated little systemic toxicity with significant prolongation of survival
			Toxicity study to study signs of toxicity for ReGel, OncoGel 1.5%, 3.0%, 6.0%	No significant difference between OncoGel 3.0% & 6.0% group	
			Efficacy study (OncoGel 3.0% and 6.0%) assessing hindlimb motor function and survival	Control group: BBB score =9.00; survival =17 days	
				Oncogel 3%: BBB score =16.80, survival =19 days	
				Oncogel 6%: BBB score =16.86, survival =24 days	
3	Abe T, 2008	Animal study, murine	21 rats with metastatic spine cancer models using paclitaxel-loaded hydroxyapatite-alginate composite beads	Disease free time	Intraosseous delivery of 2.4 wt% of paclitaxel-loaded
			3 groups	Control group =10.8 days	Hydroxyapatite-alginate composite beads prolonged the disease free time and survival time
			Group 1—local treatment group (6 rats)	Systemic Rx group =10.4 days	
			Group 2—systemic treatment group (9 rats)	Local Rx group =16.4 days	
			Group 3—control group (6 rats)	Survival	
			Assessed hindlimb motor function and survival	Control group =16 days	
				Systemic Rx group =14.2 days	
				Local Rx group =22.2 days	
				Local treatment group—140% to 150% increase in disease free time and survival time (P<0.05)	
				Systemic group—no therapeutic benefit	

Table 2 (*continued*)

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N	Study	Type	Details about study	Results	Conclusions
4	Gok B, 2009	Animal study, murine	Breast adenocarcinoma metastatic spine tumour model using OncoGel (paclitaxel releasing biodegradable polymer ReGel)	Median time to loss of ambulation (BBB scale) improved with the addition of OncoGel	Local delivery of Oncogel increased the efficacy of surgery and radiotherapy and delayed the onset of neurological decline
			Experiment 1—OncoGel following surgery versus control group	Maximum benefit observed when OncoGel to Sx plus XRT	Oncogel may be an effective adjuvant therapy in the management of metastatic spine disease
			Experiment 2—OncoGel following surgery & RT versus control group	Control =8.5 days; Sx alone =13.5 days	
			Experiment 3—OncoGel following RT versus control group		
			Assesses Hindlimb function using BBB scale	Sx + OncoGel =16 days	
				Sx + XRT =17 days;	
				Sx + XRT + OncoGel =19 days	
5	Zhao et al., 2016	Case series, human	7 patients with spinal liposacrcoma (sacrum =2; mobile =5)	3—alive with no disease	No conclusion on the effect of intra-operative cisplatin
			One en bloc resection and 6 piecemeal resections	2—recurrence requiring repeat operation	
			Intraoperative chemotherapy with cisplatin	2—death because of disease and complications	
			Surgical field is rinsed and soaked with cisplatin dissolved by desalted water		
			Follow up =24.6±13.9 months		
Recurrent tumours					
1	Duncan IC, 2004	Case report, human	36 yr/male	Good clinical recovery in terms of neurological recovery seen after at 4 weeks after first injection	Bleomycin has both antimitotic and antiangiogenic properties making it an useful agent for intralesional chemotherapy
			Angiosarcoma of midcervical spine C3, C4 with previous corpectomies, s/p chemotherapy and radiotherapy	Follow up MRI showed reduction in the volume of tumour with less compression on cord	Direct percutaneous injection of chemotherapy is an alternative method of treatment in tumours that have failed conventional treatment
			Presentation with recurrence and cord compression (quadriplegia)	No toxicity was reported	
			Total of 3 direct percutaneous intratumoral injection with 15U of Bleomycin under fluoroscopic guidance		

Table 2 (*continued*)

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N	Study	Type	Details about study	Results	Conclusions
2	Guiu S, 2009	Case report, human	46 yr/male	Marked clinical response with regression of spinal cord compression	Intratumoral chemotherapy with surgery should be considered while treating chordomas
			Recurrent chordoma C5, C6 s/p C56 corporectomy	42% decrease in tumour volume with evidence of tumour necrosis	Intratumoral chemotherapy may be a valid treatment option when surgery and radiation therapy fail
			Recurrence with cord compression and neurological deficits. Second operation with C4,5,6 corpectomy and reconstruction	No specific toxicity related to injected medicines noted	
			Residual tumour not amenable to resection		
			Carboplatin-Epinephrine solution (3 to 5 mL) under CT guidance with needles placed in the upper, middle and lower parts of tumour		
			Total of 11 injections over 18 months period		

BBB, Basso-Beattie-Bresnahan; Rx, treatment; Sx, surgery; XRT, external beam radiotherapy; s/p, status post; yr, year.

reduce residual tumour cells and thereby local recurrence. It was performed by rinsing and soaking the surgical field with cisplatin dissolved by desalted water. At the end of follow-up period (average =24.6±13.9 months), 2 patients had local recurrence requiring repeat operation, 3 patients were alive with no evidence of disease and 2 died because of disease and complications. However, there were few concerns in this study as well. Firstly, there was no standardisation of cisplatin administration following resection the study neither mentioned the dose nor there was sustained delivery of drug at the operated site. Secondly, only one application with short exposure time might not be very beneficial in eradicating the remaining tumour cells as they enter the most sensitive phase for the drug to act at different time periods. Importantly, the study did not mention any adverse effects secondary to one-time application of chemotherapy drug (34).

The possible benefits of this technique have also been shown in 2 human case reports with recurrent spinal tumours. Duncan *et al.* in his case report of recurrent angiosarcoma of C3, C4 treated previously with surgery, radiotherapy and chemotherapy noticed a good clinical improvement in terms of neurological recovery and regression of tumour size in MRI following intratumoral injection of Bleomycin. In addition, no systemic toxicity was observed due to bleomycin injection (35).

Another case report of recurrent chordoma C5, C6 treated previously by corpectomy also showed significant clinical improvement with regression of spinal cord compression and 42% reduction in the size of the tumour following intratumoral administration of carboplatin and epinephrine. No systemic toxicity to carboplatin or epinephrine was noticed (36).

Chemotherapy drugs suitable for local administration

The first report of using a chemotherapeutic agent for intratumoral delivery came from Heppner and Diemath in 1963 who used endoxan soaked spongastan (37). Since then, many chemotherapy medicines from different groups have been tested as a potential drug for local administration in a variety of tumours (24). These include vincristine (38), doxorubicin (39), bleomycin (40), cisplatin (36), carmustine (41), 5-fluorouracil (42), methotrexate (43) and paclitaxel. Among these, Paclitaxel has been shown to have significant antitumour activity in solid cancers including breast cancer. Being a taxane group drug, it has

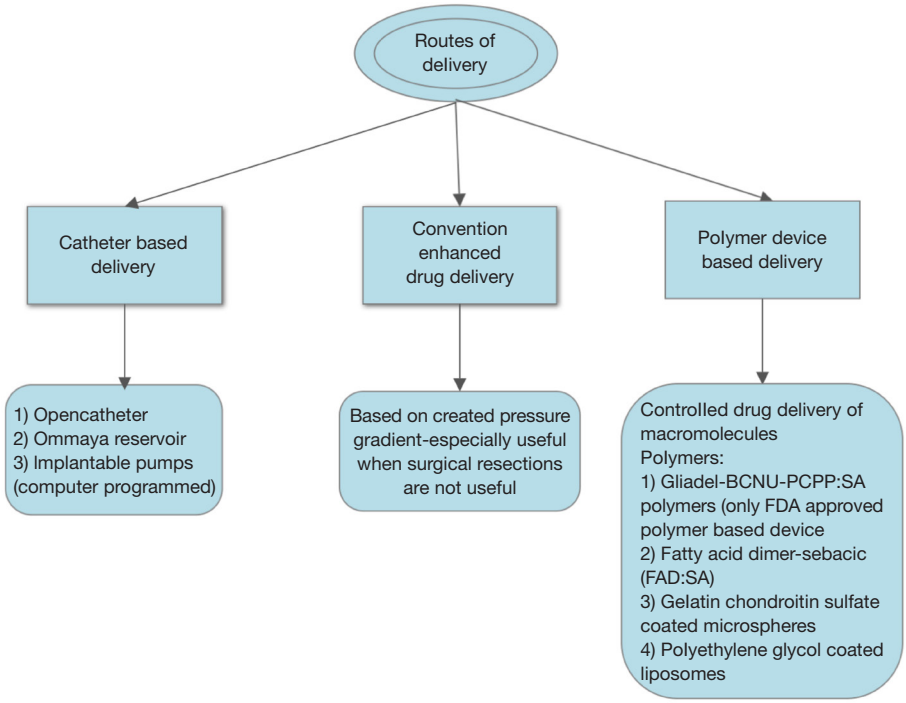

Figure 3 Categories of drug delivery methods for local administration of chemotherapy drugs.

dose dependent anti-proliferative, anti-angiogenic, anti-metastatic and apoptotic activities. Local administration of paclitaxel exhibits well balanced therapeutic effects than when administered systemically. Additionally, its radiosensitizing property is an added advantage for better local tumour control as surgery followed by radiotherapy is the usual norm for the management of spine tumours rather than an exception. Paclitaxel being extremely hydrophobic, intravenous administration is limited and in addition, a formulation containing cremophor EL has been found to cause hypersensitivity reactions. All animal studies included in the present review had used paclitaxel as the chemotherapeutic agent for local administration. However, not all chemotherapeutic drugs are amenable to a local administration. For instance, cyclophosphamide which is the most widely used anticancer agent is a poor candidate for local administration as it requires enzymatic activation to an active metabolite in the liver by the p450 cytochrome oxidase system. The parent compound as such has no antitumour activity.

Delivery modes for local administration of cancer drugs

Figure 3 outlines the various drug delivery methods that have been tried for the local administration of chemotherapy. Polymer-based delivery is more popular among the other types due to the advantage of controlled drug delivery. In 1976, Langer and Folkman introduced the polymer-based drug delivery system using the polymer Ethylene Vinyl acetate copolymer (EVAc) (44). Since then, various polymer systems have evolved for delivery of a variety of drugs including steroids and anti-inflammatories. Till this date, Gliadel, a PCPP:SA {Poly[bis(p-carboxyphenoxy propane-sebacic acid)]} polymer loaded with carmustine is the only FDA approved device approved for the treatment of gliomas. This system allows moulding into various shapes like rods, wafers, sheets and microspheres due to the requirement for high pressures and low temperatures needed for the synthesis (45). Preclinical and clinical trials have ensured the safety of this polymer and no additional toxicity was seen when combined with radiotherapy postoperatively (46). This advantage can also be exploited in the treatment of spine tumours by customising the shape of the polymer into the possible shape of the defect that will result following the excision of a tumour. Future researches on this area can result in the synthesis of these polymers which can provide structural stability as well.

Similarly, hydroxyapatite alginate composites have also been found to produce promising results as one of the best carriers for the treatment of bone diseases. Hydroxyapatite possesses osteoconductive property even in irradiated bones and is considered better than other biomaterials. Alginate possesses cell adhesion quality and sustained release of drugs. Abe *et al.*, in his 2007 murine study randomised ten rats into two groups—local treatment group and control group, and utilised paclitaxel loaded hydroxyapatite alginate gel and demonstrated that in the local treatment group, survival has increased by an average of 7.6 days in the local treatment group (21.6 days) from 14 days in the control group. Additionally, rats in local treatment group demonstrated better hindlimb motor function [using Basso-Beattie-Bresnahan (BBB) rating scale]. Another study by the same author in 2008 used paclitaxel loaded hydroxyapatite alginate beads. Twenty one rats were grouped into (I) control group; (II) local treatment group where paclitaxel loaded hydroxyapatite alginate beads were implanted intraosseously; (III) systemic group. It was found that local treatment group had 140% to 150% increase in survival and disease-free time. The same was not observed in the systemic group even after administration of 30 times higher dose (32).

Oncogel (Protherics, Inc., USA) is another polymer based drug delivery system consisting of paclitaxel-loaded in a water-soluble, biodegradable polymer (poly-DL-lactide-co-glycolide-polyethylene glycol-poly-DL-lactide-co-glycolide) with a physical property of transformation into a gel state from liquid state once the temperature exceeds 17.8 ℃. It has the advantage of sustained release of paclitaxel from the gel in a linear fashion over approximately the next 50 days (47). The combination of Oncogel's gelled state and sustained drug release from it makes it another attractive treatment option. Bagley *et al.* in 2007, used Oncogel loaded with paclitaxel in two different concentrations—3% and 6% and established that rats with Oncogel 3% and 6% had longer survival period (average of 18 days) than the control group which survived for 14 days (statistically significant $P<0.05$). In addition, more necrosis with less infiltration was seen in the group treated with 6% Oncogel than compared to other treatment groups. In addition, no signs of systemic toxicity were noted in any of the treatment groups (33). Gok *et al.*, conducted an experimental study on rats using OncoGel as an adjuvant therapy in three different sets of experiments which include (I) OncoGel following surgery versus control group; (II) OncoGel following surgery and Radiotherapy versus control group and (III) Oncogel following Radiotherapy versus control group. In each experimental group, animals which received OncoGel fared best with respect to delay in loss of hindlimb function (BBB scale). He concluded that best treatment option for spinal metastasis would be the combination of surgery with radiation and OncoGel (14).

Cancer drugs loaded cement has also been explored as one of the potential tools for both local deliveries of therapeutic substances and structural support (48,49). polymethyl methacrylate (PMMA) polymer in bone cement has been used as a carrier vehicle for drugs like antibiotics (50) and nonsteroidal anti-inflammatory drugs (NSAIDs) (51) since the 1970s. Hernigou *et al.* for the first time in 1989 proved the release of methotrexate from methotrexate loaded cement implanted in patients with bone tumours (52). It has also been demonstrated that loading of cement with antiblastic compounds like doxorubicin, cisplatin, methotrexate by *in vitro* and *in vivo* studies did not affect the polymerisation of PMMA. The addition of the drug neither altered the cytotoxic effect nor the biomechanical properties of the cement. This study has also demonstrated the cytotoxic effect of the eluted drug on osteosarcoma cell lines.

In addition to the PMMA cement, calcium phosphate cement and aluminium free glass ionomer cement have also been studied for local administration of chemotherapy.

Safety

Researches in brain tumours with interstitial or intratumoral chemotherapy have proved the safety of this method on neural tissues. Intratumoral or interstitial chemotherapy was devised to bypass the barriers [blood brain barrier, blood cerebrospinal fluid (CSF) barrier and blood tumour barrier] and deliver a high concentration of drug to the tumour locally and avoid the systemic effects of chemotherapy (23). This process has not been found to cause additional toxicity to the neural tissues. This, when extrapolated to the treatment of primary tumours and metastatic spine tumours, would most likely to be safe for the spinal cord too. In addition to the above effective similar barriers in the spinal cord, dura being a tough structure can provide additional protection to the cord from the direct cytotoxic effects of chemotherapeutic drugs. Tyler *et al.*, in his murine intramedullary gliosarcoma tumour model clearly demonstrated that OncoGel can be administered safely into the spinal cord of rats at doses unto 5 microsites of 3.0 mg/mL

of paclitaxel with significant prolongation of hindlimb motor function and survival. However, a dose of 5 mL of 6.0 mg/mL caused rapid deterioration of hindlimb motor function which can be attributed to the spinal cord edema secondary to paclitaxel (27).

The limitations of this review are all studies mentioned here determine the effect of single dose application of treatment before onset of neurological deficits. This is true to some extent when applied to the clinical setting as 15% to 40% of patients with metastatic spine tumour disease do not have an obvious motor weakness at the time of diagnosis. All studies mentioned neurological decline as a measure of therapeutic outcome rather than imaging. Further, no information is available on the status of wound healing, tumour regression following the adjuvant local chemotherapy.

Another important limitation of animal study is that it did not take into account of other important issues like instability which is more obvious in the upright human than in the quadruped rat. The complex systemic and biomechanics factors seen in human primary and metastatic spine tumours cannot be replicated in an animal model and hence the results from the animal studies cannot be directly applied to the human setting. However, they provide an important preclinical data suggesting that local administration of chemotherapy following surgical resection is likely to produce improved functional outcomes than compared to the present treatment regimen of surgery and irradiation alone or surgery and irradiation in combination (14).

Some of the animal studies included in our review have used non- human cell lines for creating tumour models in rats. There can be a significant difference in the response of tumour cells to paclitaxel which needs to be taken into account as well.

The available data from all the experimental studies on animal models provide initial evidence that local chemotherapy following surgical excision +/– radiotherapy may have an additive effect and needs to be further explored in the form of clinical trials in humans.

Similar to the local administration of chemotherapeutic agents, various immunotherapeutic agents as potential targets for intratumoral or intralesional administration are currently under trial in both preclinical and clinical settings (53). Concurrently, advances in drug delivery systems like polymersomes and nanoparticle technology will soon revolutionise the way we treat primary and metastatic spinal tumours (54). A detailed description of the above technology is beyond the scope of this article.

Conclusions

The technique of local administration of chemotherapeutic agents as an adjuvant therapy following excision of primary and metastatic spine tumours would be a novel strategy to ensure a tumour free environment. This would prove to be very useful as it reduces the chances of recurrence, reduces morbidity and potentially improves quality of life and prognosis. Future clinical trials should be conducted to prove the efficacy of this useful adjuvant treatment modality.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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